

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

## New oral anticoagulants in the management of venous thromboembolism: A major advance?

### This is the author's manuscript

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1609735> since 2016-11-04T09:55:10Z

*Published version:*

DOI:10.1016/j.ejvs.2014.07.007

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in EUROPEAN JOURNAL OF VASCULAR AND ENDOVASCULAR SURGERY, 48 (5), 2014, 10.1016/j.ejvs.2014.07.007.

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>), 10.1016/j.ejvs.2014.07.007

The publisher's version is available at:

<http://linkinghub.elsevier.com/retrieve/pii/S1078588414004067>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/>

## **New oral anticoagulants in the management of venous thromboembolism: a major advance?**

S. Sciascia, B.J. Hunt

S. Sciascia Guy's & St Thomas' Hospital, London, UK Centro di Ricerche di Immunologia Clinica ed Immunopatologia e Documentazione su Malattie Rare (CMID), Università di Torino, Turin, Italy

B.J. Hunt\* Guy's & St Thomas' Hospital, London, UK King's College, London, UK

For the last 60 years, vitamin K antagonists (VKAs) have been the only available oral anticoagulant for the primary and secondary prevention of both arterial and venous thromboembolism. However, VKAs have unpredictable pharmacokinetics as well as complex food and drug interactions leading to variable anticoagulation, and the consequent need for relatively frequent, costly, and inconvenient blood testing to monitor the drug's activity. An industry of anticoagulant clinics in both primary and secondary care has grown up to cater for those requiring monitoring. Despite this, bleeding due to VKAs has remained a major cause of iatrogenic admission to hospital.<sup>1,2</sup> One can also argue that a culture of fearfulness exists around patients receiving VKAs due to the complexity of managing these patients perioperatively, when they are ill, or receiving new medication. Moreover, in the current climate of concern about patient safety, in view of the poor safety record of VKAs, would such a drug be granted a license today? New oral anticoagulants (NOACs) have the potential to revolutionize the primary and secondary prevention of thrombosis, for they have predictable pharmacokinetics and thus are given in fixed doses and do not require monitoring.<sup>3</sup> Moreover, they have minimal interactions with drugs or diet. The prospect of a less rigid lifestyle than that required when taking VKAs and the freeing from anticoagulation monitoring has made NOACs very attractive to patients. In the current issue of *European Journal of Vascular and Endovascular Surgery*, Kakkos et al. present a systematic review and meta-analysis analysing the effectiveness and safety of NOACs compared with conventional treatment of warfarin for treatment and secondary prevention of venous thromboembolism (VTE). Pooling together data from 10 randomized controlled trials, with nearly 38,000 patients, the authors showed that in the six trials looking at treatment of acute symptomatic VTE, NOACs were equivalent in efficacy to conventional treatment with VKAs in reducing VTE recurrence. However, NOACs proved to be safer than conventional treatment because there was a significantly reduced bleeding risk. In fact, major bleeding rates fell from 1.73% with the use of VKA to 1.08% with the use of NOACs. NICE now recommend 3 months of anticoagulant treatment in those with acute provoked VTE,<sup>4</sup> and other guidelines recommend 3-6 months; but the issue of how long to continue anticoagulation in those who have had unprovoked VTE remains unresolved, with the trend being to use warfarin long-term in the majority. Three secondary prevention trials in patients with unprovoked VTE after acute treatment compared NOAC with placebo. There was a 7.2% rate of recurrence in those receiving placebo versus 1.3% in those receiving a NOAC, at the price of an increase in non-significant bleeding but not major bleeding (4.3% vs. 1.8). Overall the authors concluded NOACs conferred a net clinical benefit when compared to VKAs. Not only are NOACs attractive as regards their net clinical benefit and convenience, but a NICE Single Technology Assessment<sup>5</sup> and Lefebvre et al.<sup>6</sup> have evaluated the cost efficacy of rivaroxaban in the management and secondary prevention of VTE showing that rivaroxaban is more cost-effective (lower drug costs, fewer hospitalized days, less bleeding) than conventional treatment of low-molecularweight (LMW) heparin and VKAs in the acute treatment of VTE. Although cost-efficacy is higher than VKAs in longterm secondary use, it is still within an acceptable limit, due to the lower bleed rates and lower intracranial haemorrhage rates than VKAs.<sup>7</sup> At the time of writing, rivaroxaban and dabigatran are the only agents to be licensed in Europe for primary and secondary prevention of VTE, but it is expected that apixaban will gain a license shortly, swiftly followed by edoxaban. So while strong arguments of efficacy, safety, cost-efficacy, and patient convenience and experience for using NOACs in the acute management of VTE

now exist, there has been some reluctance to use them in many centres, with concerns related to the absence of a direct reversal agent. Antidotes are being fast tracked in development: a direct anti-Xa agent and a direct anti-dabigatran molecule are being trialled. But for now, unlike warfarin which can be reversed quickly by replacing the missing Factors II, VII, IX, and X by injection of prothrombin complex concentrates, there is no direct antidote. However, we need to remember that there is no reversing agent for LMW heparin and fondaparinux either, and yet these are widely used with fewer bleeding problems than VKAs. All the NOACs except dabigatran are direct anti-Xa agents and thus their mechanism of action is similar to LMW heparin and indeed both have similarly short half-lives. Conceptually and pragmatically it is helpful to consider that rivaroxaban, apixaban, and edoxaban are oral forms of LMW heparin. Currently supportive strategies are the mainstay of treatment of bleeding with both LMW heparins and NOACs, with discontinuation of the drug, mechanical compression, surgical haemostasis measures, and administration of transfusion support; and because the half-life of these agents is short, they will unlike warfarin disappear from the circulation quickly. Moreover, warfarin reversibility while conceptually attractive was not shown to improve outcomes in warfarin-related severe bleeding, such as intracranial haemorrhage, suggesting that anticoagulation reversal may not influence clinical outcomes if bleeding occurs.<sup>8</sup> If all supportive measures fail, then what reversal agents are available to initiate haemostasis? The use of recombinant active factor VII has had inconsistent results in clinical settings and its use is not clearly established.<sup>9</sup> Dialysis can represent an option.<sup>10</sup> However, because more than 90% of some NOACs (e.g. rivaroxaban) are bound to protein, it can be considered in selected cases only. More recently, prothrombin complex concentrates have been shown as potential antidote to reverse the effect of rivaroxaban and dabigatran.<sup>11</sup> However, in reality, it is our experience, that very few patients using these drugs routinely require an antidote to reverse the anticoagulant effects. Balancing the risk of clotting and the risk of bleeding still weighs heavily on the minds of clinicians. Knowing that evidence exists to support their effectiveness and safety for treatment and secondary prevention of VTE will certainly tip the scale in the favour of NOACs in their battle against the “VKA culture”.

## REFERENCES

- 1 Bigby J, Dunn J, Goldman L, Adams JB, Jen P, Landefeld CS, et al. Assessing the preventability of emergency hospital admissions. A method for evaluating the quality of medical care in a primary care facility. *Am J Med* 1987;83:1031e6.
- 2 Pirmohamed M, Park BK. Adverse drug reactions: back to the future. *Br J Clin Pharmacol* 2003;55:486e92.
- 3 Breen KA, Hunt BJ. The new oral anticoagulants. *Clin Med* 2011;11:467.
- 4 <http://www.nice.org.uk/guidance/CG144>. Retrieved July 16, 2014.
- 5 <http://publications.nice.org.uk/rivaroxaban-for-treatingpulmonary-embolism-and-preventing-recurrent-venousthromboembolism-ta287/sources-of-evidence-considered-bythe-committee>. Retrieved July 16, 2014.
- 6 Lefebvre P, Coleman CI, Bookhart BK, Wang ST, Mody SH, Tran KN, et al. Cost-effectiveness of rivaroxaban compared with enoxaparin plus a vitamin K antagonist for the treatment of venous thromboembolism. *J Med Econ* 2014;17:52e64.
- 7 Seaman CD, Smith KJ, Ragni MV. Cost-effectiveness of rivaroxaban versus warfarin anticoagulation for the prevention of recurrent venous thromboembolism: a U.S. perspective. *Thromb Res* 2013;132:647e51.
- 8 Dowlathshahi D, Butcher KS, Asdaghi N, Nahirniak S, Bernbaum ML, Giulivi A, et al. Canadian PCC Registry (CanPro) Investigators. Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. *Stroke* 2012;43: 1812e7.
- 9 van Ryn J, Stangier J, Haertter S, Liesenfeld KH, Wienen W, Feuring M, et al. Dabigatran etexilate: a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. *Thromb Haemost* 2010;103:1116e27.

10 Stangier J, Rathgen K, Stahle H, Mazur D. Influence of renal impairment on the pharmacokinetics and pharmacodynamics of oral dabigatran etexilate: an open-label, parallel-group, single-centre study. *Clin Pharmacokinet* 2010;49:259e68.

11 Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebocontrolled, crossover study in healthy subjects. *Circulation* 2011;124:1573e9.